EXHIBIT 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204485

NDA APPROVAL

Par Sterile Products, LLC
Attention: Mr. Gerald Vasquez
Morris Corporate Center 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA) dated September 25, 2012, received September 26, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vasostrict (vasopressin injection, USP), 20 units per mL.

We acknowledge receipt of your amendments dated October 18, November 18, December 17 and 23, 2013, and February 25, March 4, 6, 18, and 28 (two), April 7 and 14, 2014.

The October 18, 2013 submission constituted a complete response to our July 19, 2013 action letter.

This new drug application provides for the use of Vasostrict (vasopressin injection, USP) to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

A 12-month expiration dating period is granted for Vasostrict (vasopressin injection, USP), 20 units per mL, stored in the proposed container/closure system at the recommended storage condition, between 15°C and 25°C (59°F and 77°F).

We acknowledge your Safety Update submitted on October 18, 2013 and we agree that there are no novel safety concerns based on your submission.

We note that your April 14, 2014 submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on April 7, 2014 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204485**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for vasopressin was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. In the sole published prospective study of vasopressin in pediatric patients with vasodilatory shock (Choong et. al.), a total of 512 patients were screened over 4 years, in order to enroll only 69 patients. Attempts to obtain further data related to this published study were unsuccessful.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VASOSTRICT™ safely and effectively. See full prescribing information for VASOSTRICT.

Vasostrict (vasopressin injection) for intravenous use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
- Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (1)

----------DOSAGE AND ADMINISTRATION----------
- Dilute Vasostrict with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)
- Post-cardiotomy shock: 0.03 to 0.1 units/minute (2.2)
- Septic shock: 0.01 to 0.07 units/minute (2.2)

----------DOSAGE FORMS AND STRENGTHS ----------
- Injection: 20 units per mL; packaged as 1 mL per vial (3)

----------CONTRAINDICATIONS----------
- Vasostrict is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. (4)

----------WARNINGS AND PRECAUTIONS----------
- Can worsen cardiac function. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical Companies at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Pressor effects of catecholamines and Vasostrict are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasostrict. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. (7.3, 7.5)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.6)

----------USE IN SPECIFIC POPULATIONS----------
- **Pregnancy:** May induce uterine contractions. (8.1)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)
- **Geriatric Use:** No safety issues have been identified in older patients. (8.5)

Revised: 4/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasostrict™ is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

Dilute Vasostrict in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

Table 1 Preparation of diluted solutions

Fluid restriction?	Final concentration	Mix	
		Vasostrict	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 unit/mL	5 mL (100 units)	100 mL

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

2.2 Administration

The goal of treatment is optimization of perfusion to critical organs, but aggressive treatment can compromise perfusion of organs, like the gastrointestinal tract, whose function is difficult to monitor. The following advice is empirical. In general, titrate to the lowest dose compatible with a clinically acceptable response.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Injection: 20 units per mL; packaged as 1 mL per vial

4 CONTRAINDICATIONS

Vasostrict is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

Use in patients with impaired cardiac response may worsen cardiac output.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding

Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia

Gastrointestinal disorders: Mesenteric ischemia

Hepatobiliary: Increased bilirubin levels

Renal/urinary disorders: Acute renal insufficiency

Vascular disorders: Distal limb ischemia

Metabolic: Hyponatremia

Skin: Ischemic lesions

7 DRUG INTERACTIONS

7.1 Catecholamines

Use with *catecholamines* is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of Vasostrict on cardiac index and systemic vascular resistance *[see Clinical Pharmacology (12.3)]*.

7.3 Ganglionic Blocking Agents

Use with *ganglionic blocking agents* may increase the effect of Vasostrict on mean arterial blood pressure *[see Clinical Pharmacology (12.3)]*.

7.4 Furosemide

Use with *furosemide* increases the effect of Vasostrict on osmolar clearance and urine flow *[see Clinical Pharmacology (12.3)]*.

7.5 Drugs Suspected of Causing SIADH

Use with *drugs suspected of causing SIADH* (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict.

7.6 Drugs Suspected of Causing Diabetes Insipidus

Use with *drugs suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of Vasostrict.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: There are no adequate or well-controlled studies of Vasostrict in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin *[see Clinical Pharmacology (12.3)]*.

Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict may need to be up-titrated to doses exceeding 0.1 units/minute in post-cardiotomy shock and 0.07 units/minute in septic shock.
Vasostrict may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.3 Nursing Mothers

It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of Vasostrict in pediatric patients with vasodilatory shock have not been established.

8.5 Geriatric Use

Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and

younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

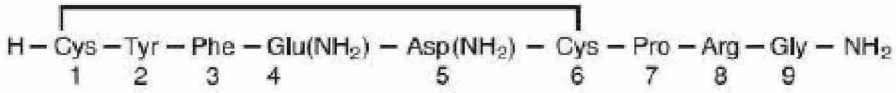
Overdosage with Vasostrict can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

Direct effects will resolve within minutes of withdrawal of treatment.

11 DESCRIPTION

Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:



Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular Weight: 1084.23

One mg is equivalent to 530 units.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The vasoconstrictive effects of vasopressin are mediated by vascular V_1 receptors. Vascular V_1 receptors are directly coupled to phopholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V_2 receptors which are coupled to adenyl cyclase.

12.2 Pharmacodynamics

At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V_1-receptors and release of prolactin and

ACTH via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. Onset of the pressor effect of vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients.

12.3 Pharmacokinetics

At infusion rates used in vasodilatory shock (0.01-0.1 units/minute) the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent $t_{1/2}$ of vasopressin at these levels is ≤10 minutes. Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of vasopressin is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxido-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Drug-Drug Interactions

Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy subjects *[see Drug Interactions (7.2)]*.

The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of vasopressin by 20% in healthy subjects *[see Drug Interactions (7.3)]*.

Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when co-administered with exogenous vasopressin in healthy subjects *[see Drug Interactions (7.4)]*.

Halothane, morphine, fentanyl, alfentanyl and sufentanyl do not impact exposure to endogenous vasopressin.

Special Populations

Pregnancy: Because of a spillover into blood of placental vasopressinase the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery the clearance of vasopressin returns to pre-conception baseline within two weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the *in vitro* bacterial mutagenicity (Ames) test and the *in vitro* Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

14 CLINICAL STUDIES

Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasostrict (vasopressin injection, USP) is supplied in vials as follows:

A carton of 25 multi-dose vials each containing vasopressin 1 mL at 20 units/mL.

Store between 15°C and 25°C (59°F and 77°F). Do not freeze.

Discard vial after 48 hours after first puncture.

NDC 42023-164-25 (carton)

PAR PHARMACEUTICAL

Manufactured by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

OS164J-01-90-01

Vasostrict is a registered trademark of Par Pharmaceutical Companies, Inc.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
04/17/2014

EXHIBIT 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204485/S-003

APPROVAL LETTER

Par Sterile Products, LLC
Attention: Carla English, Senior Manager Regulatory Affairs
One Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. English:

Please refer to your Supplemental New Drug Application (sNDA) dated November 19, 2015, received November 19, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vasostrict® (vasopressin injection, USP).

We acknowledge receipt of your amendment dated January 13, 2016 and March 10, 2016.

This "Prior Approval" supplemental new drug application provides for a change in formulation in the finished drug product and revisions to the drug product specifications.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling packaging insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-

up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204485/S-003**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

Ramesh Raghavachari -S

Digitally signed by Ramesh Raghavachari -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211793, cn=Ramesh Raghavachari -S
Date: 2016.03.18 16:19:34 -04'00'

Ramesh Raghavachari, Ph.D.
Chief, Branch I
Division of Post Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Vasostrict®
(vasopressin injection, USP)
For Intravenous Infusion

3003619

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VASOSTRICT® safely and effectively. See full prescribing information for VASOSTRICT®.

Vasostrict® (vasopressin injection) for intravenous use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

- Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (1)

----------DOSAGE AND ADMINISTRATION----------

- Dilute Vasostrict® with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)
- Post-cardiotomy shock: 0.03 to 0.1 units/minute (2.2)
- Septic shock: 0.01 to 0.07 units/minute (2.2)

----------DOSAGE FORMS AND STRENGTHS ----------

- Injection: 20 units per mL; packaged as 1 mL per vial (3)

----------CONTRAINDICATIONS----------

- Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. (4)

----------WARNINGS AND PRECAUTIONS----------

- Can worsen cardiac function. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Pressor effects of catecholamines and Vasostrict® are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasostrict®. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. (7.3, 7.5)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** May induce uterine contractions. (8.1)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)
- **Geriatric Use:** No safety issues have been identified in older patients. (8.5)

Revised: 11/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

Dilute Vasostrict® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

Table 1 Preparation of diluted solutions

Fluid restriction?	Final concentration	Mix	
		Vasostrict®	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 unit/mL	5 mL (100 units)	100 mL

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

2.2 Administration

The goal of treatment is optimization of perfusion to critical organs, but aggressive treatment can compromise perfusion of organs, like the gastrointestinal tract, whose function is difficult to monitor. The following advice is empirical. In general, titrate to the lowest dose compatible with a clinically acceptable response.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict® by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Injection: 20 units per mL; packaged as 1 mL per vial

4 CONTRAINDICATIONS

Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

Use in patients with impaired cardiac response may worsen cardiac output.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding

Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia

Gastrointestinal disorders: Mesenteric ischemia

Hepatobiliary: Increased bilirubin levels

Renal/urinary disorders: Acute renal insufficiency

Vascular disorders: Distal limb ischemia

Metabolic: Hyponatremia

Skin: Ischemic lesions

7 DRUG INTERACTIONS

7.1 Catecholamines

Use with *catecholamines* is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of Vasostrict® on cardiac index and systemic vascular resistance *[see Clinical Pharmacology (12.3)]*.

7.3 Ganglionic Blocking Agents

Use with *ganglionic blocking agents* may increase the effect of Vasostrict® on mean arterial blood pressure *[see Clinical Pharmacology (12.3)]*.

7.4 Furosemide

Use with *furosemide* increases the effect of Vasostrict® on osmolar clearance and urine flow *[see Clinical Pharmacology (12.3)]*.

7.5 Drugs Suspected of Causing SIADH

Use with *drugs suspected of causing SIADH* (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict®.

7.6 Drugs Suspected of Causing Diabetes Insipidus

Use with *drugs suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of Vasostrict®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: There are no adequate or well-controlled studies of Vasostrict® in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin *[see Clinical Pharmacology (12.3)]*.

Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict® may need to be up-titrated to doses exceeding 0.1 units/minute in post-cardiotomy shock and 0.07 units/minute in septic shock.

Vasostrict® may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.3 Nursing Mothers

It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of Vasostrict® in pediatric patients with vasodilatory shock have not been established.

8.5 Geriatric Use

Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

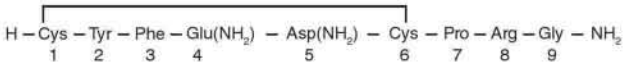
Overdosage with Vasostrict® can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

Direct effects will resolve within minutes of withdrawal of treatment.

11 DESCRIPTION

Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict® is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, Water for Injection, USP and, sodium acetate buffer adjusted to a pH of 3.8.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:



Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular Weight: 1084.23

One mg is equivalent to 530 units.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The vasoconstrictive effects of vasopressin are mediated by vascular V_1 receptors. Vascular V_1 receptors are directly coupled to phopholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V_2 receptors which are coupled to adenyl cyclase.

12.2 Pharmacodynamics

At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V_1-receptors and release of prolactin and ACTH via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. Onset of the pressor effect of vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients.

12.3 Pharmacokinetics

At infusion rates used in vasodilatory shock (0.01-0.1 units/minute) the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent $t_{1/2}$ of vasopressin at these levels is ≤10 minutes. Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of vasopressin is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxido-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Drug-Drug Interactions

Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy subjects *[see Drug Interactions (7.2)]*.

The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of vasopressin by 20% in healthy subjects *[see Drug Interactions (7.3)]*.

Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when co-administered with exogenous vasopressin in healthy subjects *[see Drug Interactions (7.4)]*.

Halothane, morphine, fentanyl, alfentanyl and sufentanyl do not impact exposure to endogenous vasopressin.

Special Populations

Pregnancy: Because of a spillover into blood of placental vasopressinase the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery the clearance of vasopressin returns to pre-conception baseline within two weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the *in vitro* bacterial mutagenicity (Ames) test and the *in vitro* Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

14 CLINICAL STUDIES

Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasostrict® (vasopressin injection, USP) is supplied in vials as follows:

A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL.

Store between 2°C and 8°C (36°F and 46°F). Do not freeze.

Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict® beyond the manufacturer's expiration date stamped on the vial.

The storage conditions and expiration periods are summarized in the following table.

	Unopened Refrigerated 2°C to 8°C (36°F to 46°F)	Unopened Room Temperature 20°C to 25°C (68°F to 77°F) Do not store above 25°C (77°F)
1 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier

NDC 42023-164-25 (carton)

Distributed by:
Par Pharmaceutical Companies, Inc.
Chestnut Ridge, NY 10977

R11/15 OS164J-01-90-04

Vasostrict® is a registered trademark of Par Pharmaceutical Companies, Inc.

EXHIBIT 3

From:	Goldberg, Brian
To:	Cade, Ashley; Rhoad, Robert; Lasky, Benjamin; Greene, Blake; Kwon, Sam; Gagliardi, Sharon; #EagleVasopressinLitigation
Cc:	ALL NA Endo Vasopressin; EXT Brian Farnan; EXT Michael Farnan; *dmoore@Potteranderson.com1; *sobyrne@potteranderson.com
Subject:	[EXT] RE: Pretrial Exchanges
Date:	Tuesday, March 17, 2020 11:36:32 AM

Ashley,

Apologies, my service email appears to have gotten stuck in my outbox.

Pursuant to the parties' agreement regarding pretrial exchanges, Par hereby discloses its narrowed list of claims that it intends to assert at trial. Par discloses this list without prejudice to its right to add to or change the asserted claims should Eagle further amend its ANDA.

'209 Patent: Claims 1, 3, 4, 5, 7
'785 Patent: Claims 1, 4, 5, 8
'526 Patent: Claim 13

Regards,

Brian

Brian Goldberg

Dechert LLP
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From: Cade, Ashley [mailto:ashley.cade@kirkland.com]
Sent: Tuesday, March 17, 2020 11:34 AM
To: Rhoad, Robert <robert.rhoad@dechert.com>; Lasky, Benjamin <blasky@kirkland.com>; Greene, Blake <Blake.Greene@dechert.com>; Kwon, Sam <sam.kwon@kirkland.com>; Gagliardi, Sharon <sharon.gagliardi@dechert.com>; #EagleVasopressinLitigation <EagleVasopressinLitigation@kirkland.com>
Cc: ALL NA Endo Vasopressin <NAEndoVasopressin@dechert.com>; EXT Brian Farnan <bfarnan@farnanlaw.com>; EXT Michael Farnan <mfarnan@farnanlaw.com>; *dmoore@Potteranderson.com1 <dmoore@Potteranderson.com>; *sobyrne@potteranderson.com <sobyrne@potteranderson.com>
Subject: RE: Pretrial Exchanges

Counsel,

Pursuant to the parties' agreement on pretrial exchanges, Par's deadline to identify claims to try at trial was 6 PM yesterday. Please let us know when Par expects to identify claims.

Best,
Ashley

Ashley Cade

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---

ashley.cade@kirkland.com

From: Rhoad, Robert <robert.rhoad@dechert.com>
Sent: Monday, March 16, 2020 10:54 AM
To: Lasky, Benjamin <blasky@kirkland.com>; Greene, Blake <Blake.Greene@dechert.com>; Kwon, Sam <sam.kwon@kirkland.com>; Gagliardi, Sharon <sharon.gagliardi@dechert.com>; #EagleVasopressinLitigation <EagleVasopressinLitigation@kirkland.com>
Cc: ALL NA Endo Vasopressin <NAEndoVasopressin@dechert.com>; EXT Brian Farnan <bfarnan@farnanlaw.com>; EXT Michael Farnan <mfarnan@farnanlaw.com>; *dmoore@Potteranderson.com1 <dmoore@Potteranderson.com>; *sobyrne@potteranderson.com <sobyrne@potteranderson.com>
Subject: [EXT] RE: Pretrial Exchanges

Ben,

Confirmed we have an agreement. Thanks,

Bob

Robert D. Rhoad

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From: Lasky, Benjamin [mailto:blasky@kirkland.com]
Sent: Monday, March 16, 2020 9:48 AM
To: Greene, Blake <Blake.Greene@dechert.com>; Kwon, Sam <sam.kwon@kirkland.com>; Gagliardi, Sharon <sharon.gagliardi@dechert.com>; #EagleVasopressinLitigation <EagleVasopressinLitigation@kirkland.com>
Cc: ALL NA Endo Vasopressin <NAEndoVasopressin@dechert.com>; EXT Brian Farnan <bfarnan@farnanlaw.com>; EXT Michael Farnan <mfarnan@farnanlaw.com>; *dmoore@Potteranderson.com1 <dmoore@Potteranderson.com>; *sobyrne@potteranderson.com <sobyrne@potteranderson.com>
Subject: RE: Pretrial Exchanges

Blake,

Based on the parties' mutual understanding of the proposal we discussed during Friday's meet-and-

EXHIBIT 4

(12) **United States Patent**
Kenney et al.

(10) **Patent No.: US 9,687,526 B2**
(45) **Date of Patent: *Jun. 27, 2017**

(54) **VASOPRESSIN FORMULATIONS FOR USE IN TREATMENT OF HYPOTENSION**

(71) Applicant: **Par Pharmaceutical, Inc.**, Chestnut Ridge, NY (US)

(72) Inventors: **Matthew Kenney**, New Haven, MI (US); **Vinayagam Kannan**, Rochester, MI (US); **Sunil Vandse**, Basking Ridge, NJ (US); **Suketu Sanghvi**, Kendall Park, NJ (US)

(73) Assignee: **PAR PHARMACEUTICAL, INC.**, Chestnut Ridge, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/289,640**

(22) Filed: **Oct. 10, 2016**

(65) **Prior Publication Data**

US 2017/0035853 A1 Feb. 9, 2017

Related U.S. Application Data

(63) Continuation-in-part of application No. 14/717,877, filed on May 20, 2015, which is a continuation of application No. 14/610,499, filed on Jan. 30, 2015, now abandoned.

(51) **Int. Cl.**

A61K 38/22	(2006.01)
A61K 9/00	(2006.01)
A61K 47/12	(2006.01)
A61K 47/02	(2006.01)
A61K 47/26	(2006.01)
A61K 31/045	(2006.01)
A61K 38/11	(2006.01)
A61K 45/06	(2006.01)
A61K 47/10	(2017.01)
A61K 9/08	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 38/22*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 31/045*** (2013.01); ***A61K 38/11*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/02*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/26*** (2013.01)

(58) **Field of Classification Search**

CPC C07K 7/16; A61K 38/11

See application file for complete search history.

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5,252,263	A	10/1993	Hope et al.
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5,288,498	A	2/1994	Stanley et al.
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(Continued)

Primary Examiner — Christina Bradley

(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

Provided herein are peptide formulations comprising polymers as stabilizing agents. The peptide formulations can be more stable for prolonged periods of time at temperatures higher than room temperature when formulated with the polymers. The polymers used in the present invention can decrease the degradation of the constituent peptides of the peptide formulations.

20 Claims, 18 Drawing Sheets

-continued

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<220> FEATURE:
<223> OTHER INFORMATION: C-term NH2

<400> SEQUENCE: 17

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What is claimed is:

1. A method of increasing blood pressure in a human in need thereof, the method comprising:

a) providing a pharmaceutical composition for intravenous administration comprising: i) from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof; ii) acetic acid; and iii) water,

wherein the pharmaceutical composition has a pH of 3.8;

b) storing the pharmaceutical composition at 2-8° C. for at least 4 weeks; and

c) intravenously administering the pharmaceutical composition to the human,

wherein the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute,

wherein the human is hypotensive,

wherein the pharmaceutical composition exhibits less than about 5% degradation after storage at 2-8° C. for about four weeks.

2. The method of claim **1**, wherein the pharmaceutical composition further comprises SEQ ID NO: 2 in an amount of about 0.01% after storage for about 4 weeks at 2-8° C.

3. The method of claim **1**, wherein the pharmaceutical composition further comprises SEQ ID NO: 3 in an amount of about 0.01% after storage for about 4 weeks at 2-8° C.

4. The method of claim **1**, wherein the pharmaceutical composition further comprises SEQ ID NO: 4 in an amount of about 0.01% after storage for about 4 weeks at 2-8° C.

5. The method of claim **1**, wherein the human's mean arterial blood pressure is increased within 15 minutes of administration.

6. The method of claim **5**, wherein the human's hypotension is associated with vasodilatory shock.

7. The method of claim **6**, wherein the vasodilatory shock is post-cardiotomy shock.

8. The method of claim **6**, wherein the vasodilatory shock is septic shock.

9. The method of claim **8**, wherein the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.07 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute.

10. The method of claim **1**, further comprising attaining a target blood pressure in the human and continuing the administration for a period of about 8 hours.

11. The method of claim **10**, further comprising, after the period of about 8 hours, reducing the administration by about 0.005 units per minute.

12. The method of claim **1**, wherein the pharmaceutical composition is stored at about 5° C.

13. The method of claim **1**, wherein the pharmaceutical composition exhibits less than 1% degradation after storage at 2-8° C. for about four weeks.

14. The method of claim **1**, wherein the pharmaceutical composition is not lyophilized.

15. The method of claim **1**, wherein the pharmaceutical composition form is not frozen.

16. The method of claim **1**, wherein the pharmaceutical composition is diluted in a diluent prior to administration to the subject.

17. The method of claim **16**, wherein the pharmaceutical composition is diluted to a concentration of from about 0.21 μg/mL to about 2.1 μg/mL of vasopressin or the pharmaceutically acceptable salt thereof.

18. The method of claim **16**, wherein the diluent is 0.9% saline.

19. The method of claim **16**, wherein the diluent is 5% dextrose in water.

20. The method of claim **1**, wherein the pharmaceutical composition further comprises chlorobutanol.

* * * * *

EXHIBIT 5

(12) **United States Patent**
Kenney et al.

(10) **Patent No.: US 9,744,209 B2**
(45) **Date of Patent: *Aug. 29, 2017**

(54) **VASOPRESSIN FORMULATIONS FOR USE IN TREATMENT OF HYPOTENSION**

(71) Applicant: **Par Pharmaceutical, Inc.**, Chestnut Ridge, NY (US)

(72) Inventors: **Matthew Kenney**, New Haven, MI (US); **Vinayagam Kannan**, Rochester, MI (US); **Sunil Vandse**, Basking Ridge, NJ (US); **Suketu Sanghvi**, Kendall Park, NJ (US)

(73) Assignee: **PAR PHARMACEUTICAL, INC.**, Chestnut Ridge, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/426,693**

(22) Filed: **Feb. 7, 2017**

(65) **Prior Publication Data**

US 2017/0157202 A1 Jun. 8, 2017

Related U.S. Application Data

(63) Continuation-in-part of application No. 15/289,640, filed on Oct. 10, 2016, which is a continuation-in-part of application No. 14/717,877, filed on May 20, 2015, which is a continuation of application No. 14/610,499, filed on Jan. 30, 2015, now abandoned.

(51) **Int. Cl.**

A61K 38/11	(2006.01)
A61K 47/12	(2006.01)
G01N 30/74	(2006.01)
G01N 30/88	(2006.01)
G01N 30/02	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 38/11*** (2013.01); ***A61K 47/12*** (2013.01); ***G01N 30/74*** (2013.01); ***G01N 30/88*** (2013.01); *G01N 2030/027* (2013.01); *G01N 2030/8831* (2013.01)

(58) **Field of Classification Search**

CPC A61K 38/11; C07K 7/16

See application file for complete search history.

(56) **References Cited**

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4,762,820	A	8/1988	Gavras
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5,250,022	A	10/1993	Chien et al.
5,252,263	A	10/1993	Hope et al.
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5,288,498	A	2/1994	Stanley et al.
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5,811,399	A	9/1998	Khavinson et al.
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5,981,474	A	11/1999	Manning et al.
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6,264,981	B1	7/2001	Zhang et al.
6,287,588	B1	9/2001	Shih et al.
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(Continued)

OTHER PUBLICATIONS

Label for Vasostrict (vasopressin injection) for intravenous use, downloaded from www.fda.gov on Mar. 21, 2017.*

AHFS Drug Information. Vasopressin. Pituitary. 2011; 68:28, 3261-3263.

Alten, et al. Early initiation of arginine vasopressin infusion in neonates after complex cardiac surgery. Pediatr Crit Care Med. May 2012;13(3):300-4. doi: 10.1097/PCC.0b013e31822f1753.

(Continued)

Primary Examiner — Christina Bradley

(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

Provided herein are peptide formulations comprising polymers as stabilizing agents. The peptide formulations can be more stable for prolonged periods of time at temperatures higher than room temperature when formulated with the polymers. The polymers used in the present invention can decrease the degradation of the constituent peptides of the peptide formulations.

13 Claims, 19 Drawing Sheets

-continued

peptide
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<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: D-Cys
<220> FEATURE:
<223> OTHER INFORMATION: C-term NH2

<400> SEQUENCE: 15

Cys Tyr Phe Gln Asn Cys Pro Arg Gly
1 5

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<220> FEATURE:
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<220> FEATURE:
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<400> SEQUENCE: 16

Cys Tyr Phe Gln Asn Cys Pro Arg Gly
1 5

<210> SEQ ID NO 17
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: D-Arg
<220> FEATURE:
<223> OTHER INFORMATION: C-term NH2

<400> SEQUENCE: 17

Cys Tyr Phe Gln Asn Cys Pro Arg Gly
1 5

What is claimed is:

1. A method of increasing blood pressure in a human in need thereof, the method comprising administering to the human a unit dosage form, wherein the unit dosage form comprises from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically acceptable salt thereof, wherein:

the unit dosage form has a pH of 3.7-3.9;

the unit dosage form further comprises impurities that are present in an amount of 0.9% - 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1;

the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute; and

the human is hypotensive.

2. The method of claim **1**, wherein the impurities comprise SEQ ID NO.: 2, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3%.

3. The method of claim **1**, wherein the impurities comprise SEQ ID NO.: 3, and SEQ ID NO.: 3 is present in the unit dosage form in an amount of 0.1% .

4. The method of claim **1**, wherein the impurities comprise SEQ ID NO.: 4, and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

5. The method of claim **1**, wherein the impurities comprise SEQ ID NO.: 7, and SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%.

6. The method of claim **1**, wherein the impurities comprise SEQ ID NO.: 10, and SEQ ID NO.: 10 is present in the unit dosage form in an amount of 0.1%.

7. The method of claim **1**, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3% and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

8. The method of claim **7**, wherein the impurities further comprise SEQ ID NO.: 3, SEQ ID NO.: 7, and SEQ ID NO.: 10, and SEQ ID NO.: 3 is present in the unit dosage form in an amount of 0.1%, SEQ ID NO.: 7 is present in the unit

dosage form in an amount of 0.3% to 0.6%, and SEQ ID NO.: 10 is present in the unit dosage form in an amount of 0.1%.

9. The method of claim **1**, wherein the human's hypotension is associated with vasodilatory shock.

10. The method of claim **9**, wherein the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.07 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute.

11. The method of claim **1**, wherein the impurities comprise a plurality of peptides, wherein the impurities are determined based on:

(a) injecting the unit dosage form into a high pressure liquid chromatography apparatus, wherein the apparatus comprises:

(i) a chromatography column containing adsorbent particles as a stationary phase;

(ii) a first mobile phase passing through the chromatography column, wherein the first mobile phase is phosphate buffer at pH 3; and

(iii) a second mobile phase passing through the chromatography column, wherein the second mobile phase is a 50:50 acetonitrile:water solution;

(b) running the unit dosage form through the chromatography column for 55 minutes;

(c) eluting the vasopressin and the plurality of peptides from the chromatography column using a gradient of the first mobile phase, and a gradient of the second mobile phase, wherein each of the first and second mobile phase are run at a flow rate of 1 mL/min through the chromatography column;

(d) passing the eluted vasopressin and the plurality of peptides through a UV detector to generate a UV spectrum of the eluted vasopressin and the plurality of peptides;

(e) identifying a peptide of the plurality of peptides based on a retention time of the peptide of the plurality of peptides relative to a standard; and

(f) calculating an amount of the peptide of the plurality of peptides based on an integration of a peak obtained for the peptide of plurality of peptides from the UV spectrum.

12. The method of claim **1**, wherein the unit dosage form further comprises sodium acetate.

13. The method of claim **1**, the unit dosage form further comprising a pH adjusting agent.

* * * * *

EXHIBIT 6

(12) **United States Patent**
Kenney et al.

(10) **Patent No.: US 9,750,785 B2**
(45) **Date of Patent: *Sep. 5, 2017**

(54) **VASOPRESSIN FORMULATIONS FOR USE IN TREATMENT OF HYPOTENSION**

(71) Applicant: **Par Pharmaceutical, Inc.**, Chestnut Ridge, NY (US)

(72) Inventors: **Matthew Kenney**, New Haven, MI (US); **Vinayagam Kannan**, Rochester, MI (US); **Sunil Vandse**, Basking Ridge, NJ (US); **Suketu Sanghvi**, Kendall Park, NJ (US)

(73) Assignee: **PAR PHARMACEUTICAL, INC.**, Chestnut Ridge, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/426,703**

(22) Filed: **Feb. 7, 2017**

(65) **Prior Publication Data**

US 2017/0157203 A1 Jun. 8, 2017

Related U.S. Application Data

(63) Continuation-in-part of application No. 15/289,640, filed on Oct. 10, 2016, which is a continuation-in-part of application No. 14/717,877, filed on May 20, 2015, which is a continuation of application No. 14/610,499, filed on Jan. 30, 2015, now abandoned.

(51) **Int. Cl.**

A61K 38/11	(2006.01)
A61K 47/12	(2006.01)
G01N 30/74	(2006.01)
G01N 30/88	(2006.01)
G01N 30/02	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 38/11*** (2013.01); ***A61K 47/12*** (2013.01); ***G01N 30/74*** (2013.01); ***G01N 30/88*** (2013.01); *G01N 2030/027* (2013.01); *G01N 2030/8831* (2013.01)

(58) **Field of Classification Search**

CPC A61K 38/11; C07K 7/16

See application file for complete search history.

(56) **References Cited**

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6,187,756	B1	2/2001	Lee et al.
6,201,072	B1	3/2001	Rathi et al.
6,264,981	B1	7/2001	Zhang et al.
6,287,588	B1	9/2001	Shih et al.
6,589,549	B2	7/2003	Shih et al.
6,592,894	B1	7/2003	Zarif et al.
6,630,486	B1	10/2003	Royer
6,720,001	B2	4/2004	Chen et al.

(Continued)

OTHER PUBLICATIONS

Label for Vasostrict (vasopressin injection) for intravenous use, downloaded from www.fda.gov on Mar. 21, 2017.*

AHFS Drug Information. Vasopressin. Pituitary. 2011; 68:28, 3261-3263.

Alten, et al. Early initiation of arginine vasopressin infusion in neonates after complex cardiac surgery. Pediatr Crit Care Med. May 2012;13(3):300-4. doi: 10.1097/PCC.0b013e31822f1753.

Angus, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. Jul. 2001;29(7):1303-10.

(Continued)

Primary Examiner — Christina Bradley

(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

Provided herein are peptide formulations comprising polymers as stabilizing agents. The peptide formulations can be more stable for prolonged periods of time at temperatures higher than room temperature when formulated with the polymers. The polymers used in the present invention can decrease the degradation of the constituent peptides of the peptide formulations.

11 Claims, 19 Drawing Sheets

-continued

<211> LENGTH: 9
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
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<223> OTHER INFORMATION: D-Cys
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<400> SEQUENCE: 15

Cys Tyr Phe Gln Asn Cys Pro Arg Gly
1 5

<210> SEQ ID NO 16
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1 5

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<400> SEQUENCE: 17

Cys Tyr Phe Gln Asn Cys Pro Arg Gly
1 5

What is claimed is:

1. A pharmaceutical composition comprising, in a unit dosage form, from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof, wherein the unit dosage form further comprises impurities that are present in an amount of 0.9% to 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1, and wherein the unit dosage form has a pH of 3.7-3.9.

2. The pharmaceutical composition of claim **1**, wherein the impurities comprise a plurality of peptides, wherein the impurities are determined based on:

(a) injecting the unit dosage form into a high pressure liquid chromatography apparatus, wherein the apparatus comprises:

(i) a chromatography column containing adsorbent particles as a stationary phase;

(ii) a first mobile phase passing through the chromatography column, wherein the first mobile phase is phosphate buffer at pH 3; and

(iii) a second mobile phase passing through the chromatography column, wherein the second mobile phase is a 50:50 acetonitrile:water solution;

(b) running the unit dosage form through the chromatography column for 55 minutes;

(c) eluting the vasopressin and the plurality of peptides from the chromatography column using a gradient of the first mobile phase, and a gradient of the second mobile phase, wherein each of the first and second mobile phase are run at a flow rate of 1 mL/min through the chromatography column;

(d) passing the eluted vasopressin and the plurality of peptides through a UV detector to generate a UV spectrum of the eluted vasopressin and the plurality of peptides;

(e) identifying a peptide of the plurality of peptides based on a retention time of the peptide of the plurality of peptides relative to a standard; and

(f) calculating an amount of the peptide of the plurality of peptides based on an integration of a peak obtained for the peptide of plurality of peptides from the UV spectrum.

3. The pharmaceutical composition of claim **1**, wherein the impurities comprise SEQ ID NO.: 2, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1 to 0.3%.

4. The pharmaceutical composition of claim **1**, wherein the impurities comprise SEQ ID NO.: 3, and SEQ ID NO.: 3 is present in the unit dosage form in an amount of 0.1%.

5. The pharmaceutical composition of claim **1**, wherein the impurities comprise SEQ ID NO.: 4, and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

6. The pharmaceutical composition of claim **1**, wherein the impurities comprise SEQ ID NO.: 7, and SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%.

7. The pharmaceutical composition of claim **1**, wherein the impurities comprise SEQ ID NO.: 10, and SEQ ID NO.: 10 is present in the unit dosage form in an amount of 0.1%.

8. The pharmaceutical composition of claim **1**, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3% and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

9. The pharmaceutical composition of claim **8**, wherein the impurities further comprise SEQ ID NO.: 3, SEQ ID NO.: 7, and SEQ ID NO.: 10, and SEQ ID NO.: 3 is present in the unit dosage form in an amount of 0.1%, SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%, and SEQ ID NO.: 10 is present in the unit dosage form in an amount of 0.1%.

10. The pharmaceutical composition of claim **1**, further comprising sodium acetate.

11. The pharmaceutical composition of claim **1**, the unit dosage form further comprising a pH adjusting agent.

* * * * *

EXHIBIT 7

From:	Gagliardi, Sharon
To:	Citro, Christopher J.; Kwon, Sam; #EagleVasopressinLitigation; *sobyrne@potteranderson.com; *dmoore@Potteranderson.com1; *bpalapura@potteranderson.com; Lasky, Benjamin; Wacker, Jeanna; Parrado, Alvaro; jbuckley@potteranderson.com; Lefkowitz, Jay P.
Cc:	ALL NA Endo Vasopressin; EXT Michael Farnan; EXT Brian Farnan; Rhoad, Robert; Goldberg, Brian
Subject:	[EXT] RE: Par Sterile Products, LLC, et al. v. Eagle Pharmaceuticals, Inc. - Par"s Interrogatory Responses
Date:	Friday, September 6, 2019 5:46:08 PM
Attachments:	Par-Eagle -- Par_s Supplemental Responses to Rogs 14 17-19 23-24.pdf

Confidential – Pursuant to Protective Order

Christopher,

We write in reply to your email and attached letter of August 30. Addressing the issues in the order you raised them:

Interrogatory Nos. 5, 6, 10, 12 & 13: You assert that Par's responses to these interrogatories are deficient because they fail to address the '239 patent and because Par's claim as to that patent has not yet been dismissed. However, Par has agreed to dismiss that claim, and we sent you a draft stipulation dismissing that claim with prejudice on Tuesday, as Eagle requested. There are no longer any ripe disputed issues regarding infringement or validity of that patent.

Interrogatory Nos. 15, 19 & 23-24: As noted in Mr. Rhoad's earlier letter, in the interest of compromise and to avoid burdening the court with motion practice, we have agreed to Eagle's proposed resolution of the "sub-part" issue. Accordingly, we serve herewith further supplemental responses to these interrogatories.

Interrogatory Nos. 14 & 17: See attached further supplemental responses to these interrogatories.

Interrogatory No. 18: See attached further supplemental response to this interrogatory.

Par's Validity Contentions: The alleged deficiencies you identify go to the substantive merit of the contentions set forth in Par's Validity Contentions, not to the sufficiency of the disclosures. Moreover, these are disclosures which set forth Par's responsive contentions with respect to the invalidity defenses raised in Eagle's Invalidity Contentions. They are not intended or required to be a substitute for expert reports and disclosures on these issues, which will set forth the expert's opinions regarding validity, as well as the bases therefor. With respect to the criticality of the recited pH values, for example, as Par has explained, its contention is that those values are critical to the stability and impurity profile of the claimed vasopressin formulations. Par has also cited evidence in support of the criticality of pH to stability and impurity levels and described the advantages afforded by the claimed inventions with respect to stability and impurity levels. See also Par's supplemental interrogatory responses. Par's disclosures more than adequately provide notice to Eagle of its rebuttal contentions to Eagle's invalidity contentions.

Finally, with respect to Mr. Kwon's email from yesterday, Par's responses to Interrogatory Nos. 5 and 10 speak for themselves. For the avoidance of doubt, Par does not contend in this litigation that the original formulation of Vasostrict, as approved on April 17, 2014, embodies any claim of the patents

at issue that Par asserts.

Regards,
Sharon

Sharon K. Gagliardi

Dechert LLP
+1 215 994 2278 Direct
sharon.gagliardi@dechert.com
dechert.com

From: Citro, Christopher J. [mailto:christopher.citro@kirkland.com]
Sent: Wednesday, September 4, 2019 6:07 PM
To: Rhoad, Robert <robert.rhoad@dechert.com>; Kwon, Sam <sam.kwon@kirkland.com>; Goldberg, Brian <Brian.Goldberg@dechert.com>; Gagliardi, Sharon <sharon.gagliardi@dechert.com>
Cc: *sobyrne@potteranderson.com <sobyrne@potteranderson.com>; *dmoore@Potteranderson.com1 <dmoore@Potteranderson.com>; *bpalapura@potteranderson.com <bpalapura@potteranderson.com>; #EagleVasopressinLitigation <EagleVasopressinLitigation@kirkland.com>; ALL NA Endo Vasopressin <NAEndoVasopressin@dechert.com>; EXT Michael Farnan <mfarnan@farnanlaw.com>; EXT Brian Farnan <bfarnan@farnanlaw.com>
Subject: RE: Par Sterile Products, LLC, et al. v. Eagle Pharmaceuticals, Inc. - Par's Interrogatory Responses

Bob,

We write in response to your August 30, 2019 letter regarding Par's interrogatory responses. We appreciate Par's willingness to compromise and avoid burdening the Court with this matter and Par's agreement to supplement its responses to Interrogatory Nos. 14, 17, and 18.

For the avoidance of doubt, however, we note that Eagle's proposal concerns only the sub-parts issue for Interrogatory Nos. 15, 19, 23, and 24. Specifically, Eagle agrees to narrow Interrogatory No. 15 to remove three of the four alleged subparts, as proposed in our August 20, 2019 Letter, if Par agrees to withdraw its objections based on the number of interrogatories and provide substantive responses to Interrogatory Nos. 19, 23, and revised Interrogatory No. 24. We understand based on your letter that Par is willing to agree to this compromise proposal to resolve the sub-parts issue. Please confirm that is the case.

Eagle's compromise proposal does not, however, resolve or in any way affect the outstanding deficiencies in Par's responses to Interrogatory Nos. 1–18 that we have previously identified, including Par's deficient responses to Eagle's invalidity contentions, as set forth in our August 30, 2019 letter. Please provide Par's positions on those issues.

Best,

EXHIBIT 8

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 9

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 10

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 11

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 12

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 13

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204485/S-002

SUPPLEMENT APPROVAL

PAR Sterile Products, LLC
Attention: Gerald Vasquez, Sr. Manager Regulatory Affairs
One Upper Pond Road
Building D, 3rd floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your Supplemental New Drug Application (sNDA) dated February 12, 2015, received February 12, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vasostrict (vasopressin) Injection.

We acknowledge receipt of your amendments dated March 13, 2015, April 17, 2015 and May 5, 2015.

This "Changes Being Effected in 30 Days" supplemental new drug application provides for 12 months room temperature storage following storage at refrigerated conditions for up to 24 months.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended. We remind you of your following commitments:

1) To update your content of labeling and carton label per our Information Request dated May 5, 2015.
2) To continue in-use stability studies to confirm product quality after 12 months room temperature storage following storage at refrigerated conditions.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be revised per your May 5, 2015 commitment, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, annual reportable changes, not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are revised per your May 5, 2015 commitment, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204485/S-002**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

Wendy I. Wilson -S

Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S
Date: 2015.05.07 10:24:04 -04'00'

Wendy Wilson-Lee, PhD
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton Labeling

Vasostrict®
(vasopressin injection, USP)
For Intravenous Infusion

3003373B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VASOSTRICT® safely and effectively. See full prescribing information for VASOSTRICT.

Vasostrict (vasopressin injection) for intravenous use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

- Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (1)

----------DOSAGE AND ADMINISTRATION----------

- Dilute Vasostrict with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)
- Post-cardiotomy shock: 0.03 to 0.1 units/minute (2.2)
- Septic shock: 0.01 to 0.07 units/minute (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 20 units per mL; packaged as 1 mL per vial (3)

----------CONTRAINDICATIONS----------

- Vasostrict is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. (4)

----------WARNINGS AND PRECAUTIONS----------

- Can worsen cardiac function. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Pressor effects of catecholamines and Vasostrict are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasostrict. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. (7.3, 7.5)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** May induce uterine contractions. (8.1)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)
- **Geriatric Use:** No safety issues have been identified in older patients. (8.5)

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

Dilute Vasostrict in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

Table 1 Preparation of diluted solutions

Fluid restriction?	Final concentration	Mix	
		Vasostrict	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 unit/mL	5 mL (100 units)	100 mL

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

2.2 Administration

The goal of treatment is optimization of perfusion to critical organs, but aggressive treatment can compromise perfusion of organs, like the gastrointestinal tract, whose function is difficult to monitor. The following advice is empirical. In general, titrate to the lowest dose compatible with a clinically acceptable response.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Injection: 20 units per mL; packaged as 1 mL per vial

4 CONTRAINDICATIONS

Vasostrict is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

Use in patients with impaired cardiac response may worsen cardiac output.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding

Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia

Gastrointestinal disorders: Mesenteric ischemia

Hepatobiliary: Increased bilirubin levels

Renal/urinary disorders: Acute renal insufficiency

Vascular disorders: Distal limb ischemia

Metabolic: Hyponatremia

Skin: Ischemic lesions

7 DRUG INTERACTIONS

7.1 Catecholamines

Use with *catecholamines* is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of Vasostrict on cardiac index and systemic vascular resistance *[see Clinical Pharmacology (12.3)]*.

7.3 Ganglionic Blocking Agents

Use with *ganglionic blocking agents* may increase the effect of Vasostrict on mean arterial blood pressure *[see Clinical Pharmacology (12.3)]*.

7.4 Furosemide

Use with *furosemide* increases the effect of Vasostrict on osmolar clearance and urine flow *[see Clinical Pharmacology (12.3)]*.

7.5 Drugs Suspected of Causing SIADH

Use with *drugs suspected of causing SIADH* (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict.

7.6 Drugs Suspected of Causing Diabetes Insipidus

Use with *drugs suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of Vasostrict.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: There are no adequate or well-controlled studies of Vasostrict in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin *[see Clinical Pharmacology (12.3)]*.

Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict may need to be up-titrated to doses exceeding 0.1 units/minute in post-cardiotomy shock and 0.07 units/minute in septic shock.

Vasostrict may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.3 Nursing Mothers

It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of Vasostrict in pediatric patients with vasodilatory shock have not been established.

8.5 Geriatric Use

Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

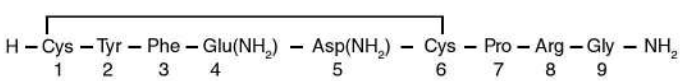
Overdosage with Vasostrict can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

Direct effects will resolve within minutes of withdrawal of treatment.

11 DESCRIPTION

Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:



Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular Weight: 1084.23

One mg is equivalent to 530 units.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The vasoconstrictive effects of vasopressin are mediated by vascular V_1 receptors. Vascular V_1 receptors are directly coupled to phopholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V_2 receptors which are coupled to adenyl cyclase.

12.2 Pharmacodynamics

At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V_1-receptors and release of prolactin and ACTH via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. Onset of the pressor effect of vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients.

12.3 Pharmacokinetics

At infusion rates used in vasodilatory shock (0.01-0.1 units/minute) the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent $t_{1/2}$ of vasopressin at these levels is ≤10 minutes. Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of vasopressin is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxido-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Drug-Drug Interactions

Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy subjects *[see Drug Interactions (7.2)]*.

The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of vasopressin by 20% in healthy subjects *[see Drug Interactions (7.3)]*.

Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when co-administered with exogenous vasopressin in healthy subjects *[see Drug Interactions (7.4)]*.

Halothane, morphine, fentanyl, alfentanyl and sufentanyl do not impact exposure to endogenous vasopressin.

Special Populations

Pregnancy: Because of a spillover into blood of placental vasopressinase the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery the clearance of vasopressin returns to pre-conception baseline within two weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the *in vitro* bacterial mutagenicity (Ames) test and the *in vitro* Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

14 CLINICAL STUDIES

Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasostrict (vasopressin injection, USP) is supplied in vials as follows:

A carton of 25 multi-dose vials each containing vasopressin 1 mL at 20 units/mL.

Store between 2°C and 8°C (36°F and 46°F). Do not freeze.

Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict beyond the manufacturer's expiration date stamped on the vial.

Discard vial after 48 hours after first puncture.

The storage conditions and expiration periods are summarized in the following table.

	Unopened Refrigerated	Unopened Room Temperature	Opened (After First Puncture)
1 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	48 hours

NDC 42023-164-25 (carton)

Manufactured by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

R03/15 OS164J-01-90-03

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EXHIBIT 14

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 15

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 16

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 17

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 18

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY